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10/535,442	05/19/2005	Stina Roth	014975-119	8832

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
11/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,442	ROTH ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) *6,11,12,14,15 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,13,23 and 24* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 8/20/2007.

The amendments to the specification have overcome the sequence compliance issues as well as objection to hyperlinks in the specification.

This action is FINAL.

Election/Restrictions

The applicants have continues their traverse of lack of unity presented in the restriction requirement and the first action on the merits. The response asserts that Warrens's teaching of SEQ ID NO 3 and SEQ ID NO 4 comprising ATA and CCGC near the 3' ends. The response asserts that the SEQ ID NO 3 and SEQ ID NO 4 comprising ATA and CCGC are not functional fragments of a primer as they, "must comprise at least enough of the recited primer sequence to function as a primer for amplification of the sequences which the recited primer sequence as a whole amplifies." This argument has been thoroughly reviewed but is not considered persuasive as the claims merely require primers comprising a functional fragment of SEQ ID 76 and 77. The claim does not require the primers consist of SEQ ID NO 76 and 77, or that the primers are functional fragments of SEQ ID NO 76 and 77.. Further, the specification does not specifically define a functional fragment or complementary sequence. Thus a functional fragment can be of any length and a complementary sequences can have any percent identity.

Claims 6, 11 and 12 are withdrawn from consideration as beyond the scope of the elected invention as they require all of the probes.

This application contains claims 6, 11, 12 are drawn to an invention nonelected with traverse in the reply filed on 5/29/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Maintained rejections

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-5, 7-10, 13 and 23-24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 7-10, 13 and 23-24 are indefinite because it lacks a positive active step relating back to the preamble. The preamble recites a method of detecting and identifying bacterial species, however the last positive active step is drawn to detecting the formation of possible hybridization complex. Therefore it is unclear as to whether the method is drawn to of detecting and identifying bacterial species or to detecting the formation of possible hybridization complex.

Response to arguments

The response of 5/29/2007 traverse this rejection as the recited steps are sufficient to accomplish of the purpose stated in the preamble. This argument has been thoroughly reviewed but is not considered persuasive because the preamble is drawn to

a method of diagnosing, however the last active step is detecting. Thus there is no diagnostic step, so it is unclear if the claims are drawn to diagnosing or detecting.

New Rejections necessitated by Amendment

3. Claims 1-5, 7-13 and 23-24 recites the limitation "said primers" in the 5th line of a). However only "DNA primers" are recited previously in the claim. This rejection can easily be overcome by amending the claims to recite, "said DNA primers". There is insufficient antecedent basis for this limitation in the claim.

Claim Objections

Claim 5 is objected to because they specifically recite nonelected subject matter. The claims require "a combination of oligonucleotide probes comprises all or a portion of the sequences identified with SEQ ID No 1 to 69". As stated in the response to the restriction filed 11/17/2006, applicant has elected a specific combination of SEQ ID NO 24. Applicant should amend the claims so that the claims are directed to the elected invention of the specific combination of genes.

Prior to allowance of these claims, the non-elected subject matter will be required to be deleted from the claims

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Haung (US Patent 5,645,994, Issued 1997).

Claim 1 recites, "a functional fragments" in reference to SEQ ID NOs 76 and 77. The specification does not specifically define a functional fragment, thus a functional fragment is broadly interpreted to be at least a single nucleotide.

With regards to claim 1, Huang teaches a method of identifying species of bacteria in a sample by amplification with universal primers based on consensus amino acid sequences which flank variable amino acid sequences (see abstract). Haung further teaches a method of designing universal primer that amplify parE and gyrB (see column 6 lines 28-65), these universal primers would identify the sequences that SEQ ID NO 76 and 77 would identify and comprise functional fragments of SEQ ID NO 76 and 77. Haung further teaches the use of universal primer compositions to amplify gyrB and parE sequences (see column 14, lines 16-19). Haung further teaches the use of nested primers to specifically distinguish between closely related species (see column 15 lines 27-35). The nested probes are thus the equivalents of the probes claimed.

Haung thus teaches a method of amplification and identification of bacterial species by hybridizing of nested primers with amplification products from universal primers. The nested primers of Haung are used to identify specific species of bacteria, and are thus equivalent to the probes of the claim. Haung's method of nested PCR is contacting amplification products with a desired number of oligonucleotide probes, and detection of hybridization complexes would be the presence of extension products.

With regards to claim 2, Haung further teaches the use of universal primer compositions to amplify gyrB and parE sequences due to their sequence similarities (see column 14, lines 16-19). Haung further teaches identification of legionella pneumophila (SEQ ID NO 70), which is a bacteria that infects the respiratory tract.

With regards to claim 4, Haung et al teaches the use of primers of 15 to 36 nucleotides in length (see column 7, lines 22-25).

Response to arguments

The response of 5/29/2007 asserts on page 14, that the broad interpretation of a functional fragment requires a single nucleotide would not function as a primer. This argument has been thoroughly reviewed but is not persuasive, because the claims nor the specification set forth the requirement that the functional fragment be a primer. The claim requires a primer comprising a functional fragment, as such the primer taught by Haung comprise a functional fragment of SEQ ID NO 76 and 77.

The response of 5/29/2007 further references Hogan and Sharrocks references to demonstrate that primers should be 15-20 nucleotides and 75-100% homologous. These arguments have been thoroughly reviewed but are not found persuasive, because Haung teaches the "primers are oligonucleotides of about 15 to 36 nucleotides' (see column 7, lines 23-25). Further the claims do not require primers of a certain length or homology, but primers comprising a complement or functional fragment of SEQ ID NO 76 and 77, which Haung teaches.

The response further asserts on page 15 that Haung teaches designing primers without referencing a specific sequence. This argument has been thoroughly reviewed

but is not found persuasive because Huang et al teaches specific primer sequence in figure 3, as well as SEQ ID NO 196-207. All these primer sequence comprise a specific nucleic acid sequence, which is a functional fragment or a complement of SEQ ID NO 76 and 77. It is noted that the instant specification does not define or teach a specific percent identity required in a complement and thus a single nucleotide is sufficiently complementary.

The response further asserts that the instant claims are drawn to specific primers not the universal primers taught by Huang for diagnosis. This argument has been thoroughly reviewed but is not considered persuasive because the claims do not require a specific primer pairs, but primers comprising SEQ ID NO 76 and 77 or complements thereof, or functional fragments. Thus the claims are broadly drawn to any primers that can be considered to comprise a functional fragment or complement. All the primers taught by Huang meet the broad requirements set forth in the claim. Further the claims do not require diagnosis, but merely detection.

The response states, "Huang et al describes primers for gyrB/gyrE." The response continues to state that the examiner has not presented a comparison of Huang primers and SEQ ID NO 76 and 77. As the claims do not require a sequence consisting of SEQ ID NO 76 and 77, but primers comprising functional fragments or complements thereof, the examiner has denoted the primers contain nucleic acids and thus inherently contain at least 1 nucleotide that is complementary to or a fragment of SEQ ID NO 76 and 77. SEQ ID NO 198 of Huang teaches AGCC which is the

complement of THGG of SEQ ID NO 76. SEQ ID NO 199 teaches AAC with are HAC of SEQ ID NO 77.

Thus Huang doe teach each and every limitation of the claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 3, 7, 8, 10, 13, are rejected under 35 U.S.C. 103(a) as being unpatentable over Haung (US Patent 5645994, Issued 1997) in view of Voelker (US patent publication 2004/0048281, filed March 23, 2001).

Huang teaches a method of identifying species in a sample by amplification with universal primers based on consensus amino acid sequences which flank variable amino acid sequences (see abstract). Haung further teaches a method of designing universal primer (see column 6 lines 28-65); these universal primers are minimally, functional fragments that identify the sequence that SEQ ID NO 76 and 77 detect. Haung further teaches the use of universal primer compositions to amplify gyrB and parE sequences (see column 14, lines 16-19). Haung further teaches the use of nested primers to specifically distinguish between closely related species (see column 15 lines 27-35).

Haung does not teach the amplification of the hypervariable region of gyrB or parE in Staphylococcus aureus. Haung does not teach the use of a solid support.

However, Voelker et al teaches amplification of gram-positive bacteria, Staphylococcus aureus gyrB (see figure 1B, lane 3, and paragraph 0025) and parE (see figure 2B, lane 3, and paragraph 0026). Voelker teaches that most clinical samples are from gram-positive bacteria (see paragraph 0004). Voelker teaches the use of degenerate primers for the identification of quinolone resistance determining regions across phylogenetic ranges of prokaryotes (see paragraph 0001, last sentence) for diagnosis, prognosis, therapy and drug discovery (see paragraph 0024).

Further, Voelker et al teaches, "a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/polynucleotide sequences for hybridization and identification." The solid surface with immobilized probes is a microarray (see paragraph 0024).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the Haung method of detecting bacterial species to amplify gyrB and parE to identify Staphylococcus aureus and use a solid support as taught by Voelker. The ordinary artisan would be motivated improve Haung's method of bacterial detection to identify Staphylococcus aureus and use solid supports as taught Voelker because Voelker teaches gram positive bacteria are the most clinically relevant. This would allow proper diagnosis and treatment of these gram-positive bacteria. Further the use of the probes on solid supports as Voelker teaches would decrease the use of reagents and increase the speed of detection.

Response to arguments

8. The response of 5/29/2007 asserts that Voelker does not anticipate the instant claims. This argument has been thoroughly reviewed but is not considered persuasive because the response is arguing the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further the response asserts that Voelker teaches amplification of a gene other than the area of the instant invention. This argument has been thoroughly reviewed but is not found persuasive because Voelker teaches amplification of gyrB (see paragraph 0025). First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding amplifying different areas are assertions and are not backed by evidence. Further the claim merely requires the amplification of the hypervariable region of gyrB, but does not set forth a specific definition of the hypervariable region. Thus this rejection is maintained.

The combination of Huang in view of Voelker does render the instant claims obvious.

9. Claims 4, 5 and 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haung (US Patent 5645994, Issued 1997) in view of Hogan et al (US Patent 5541308) and Hopewell et al (Journal of Bacteriology (1990), volume 172, pages 3481-3484)

Huang teaches a method of identifying species in a sample by amplification with universal primers based on consensus amino acid sequences, which flank variable amino acid sequences (see abstract). Haung further teaches a method of designing universal primer (see column 6 lines 28-65), these universal primers are minimally, functional fragments of SEQ ID NO 76 and 77. Haung further teaches the use of universal primer compositions to amplify gyrB and parE sequences (see column 14, lines 16-19

Haung does not teach the probe of the comprising all or a portion of SEQ ID NO 24.

However, Hogan et al teaches probe design for detection of specific sequences (see abstract). Hogan teaches identification of variable regions (see column 6, lines 3-55). Hogan teaches alignment of these variable regions (see column 6 line 67—column 7, line 8). Hogan further teaches probes should be positioned to minimize stability of probe:nontarget hybrids, by avoiding GC rich regions and areas of frequent mutation (see column 7 lines 10-15). Hogan teaches the use of synthetic oligonucleotide probes of 15-50 base pairs (see column 10, lines 40-45). Hogan further teaches maximizing

stability of probe target hybrid, by avoiding long AT sequences and terminating hybrids with G:C base pairing and the appropriate T_m(see column 7 lines 16-19). Hogan further teaches targeting sequences known to have secondary structure issues and probes that are self-complementary should be avoided (see column 7, lines 20-29).

Hopewell teaches sequence of Staphylococcus aureus gyrB, which comprises SEQ ID NO 24, (see figure 3B). Hopewell teaches that quinolone resistant Staphylococcus aureus are a major medical problem and this resistance is due to mutations in the DNA gyrase enzyme (see page 3481, 1st column, 1st paragraph).

Designing probes, which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes, see Hogan. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of probes drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design probes As discussed above, the ordinary artisan would be motivated to have designed and tested new probes to obtain additional oligonucleotides that function to detect specific hypervariable regions of bacteria and identify oligonucleotides with improved properties. The ordinary artisan would have a reasonable expectation of success of obtaining additional probes from within the sequences provided by Haung. Thus, for the reasons provided above, the ordinary artisan would have designed additional probes using the teachings in the art at the time

the invention was made. The claimed SEQ ID NOs are obvious over the cited prior art, absent secondary considerations.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the sequences taught by Hopewell and the probe design method of Hogan to make probes to detect bacterial species based on the gyrB. The ordinary artisan would thus design a probe comprising SEQ ID NO 24 or a functional fragment of SEQ ID NO 24. The ordinary artisan would be motivated to use the sequence taught by Hopewell to design probes by Hogan's method of probe design to identify mutations that result in quinolone resistance because Hopewell teaches this is a serious medical problem and proper identification would allow efficient treatment.

Response to arguments

The response of 5/29/2007 continues to argue that the claims require a primer that is a functional fragment. This argument has been reviewed above, briefly the claims require a primer comprising a functional fragment or a complement thereof of SEQ ID NO 76 and 77. Any primer comprising nucleic acids would meet the broad limitations.

Further the response asserts that Hopewell does not teach a sequence of the presently claimed method. This argument has been thoroughly reviewed but is not found persuasive because the claim is drawn to, " wherein said combination of oligonucleotide probes comprises all or a portion of the sequences identified with SEQ ID NO: 1 to 69, and/or complementary sequences hereof, or functional fragments thereof." Thus the claims broadly encompass any nucleic acids. Further Hopewell

teaches cloning and sequencing the gyrB gene from S. Aureus (see page 3481, 2nd column, 2nd full paragraph).

Examiner appreciates the clarification on quinolone resistance in the response of 5/29/2007.

The claims are thus obvious over Huang, Hogan and Hopewell.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Haung (US Patent 5645994, Issued 1997) and Voelker (US patent publication 2004/0048281, filed March 23, 2001) as applied to claim 7 above, and further in view of Southern et al (Nature Genetics supplement (1999), volume 21 pages 5-9).

The teachings of Haung in view of Voelker are set forth above.

Haung and Voelker teach the use of a solid support, however they do not teach the use of treated glass as a solid substrate.

Southern et al teach that treated glass is a preferred solid support as it allows the synthesis of oligonucleotides (see page 7, 1st column line 30-36). Southern teaches that the use of glass has the advantages that liquid cannot penetrate glass, it enhances the rate of hybridization, improves washing by improving diffusion.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the treated glass support taught by Southern as the solid support of Haung in view of Voelker. The ordinary artisan would be motivated to use the treated glass support of Southern because Southern teaches glass improves washing; rate of hybridization and liquid cannot penetrate it. The use of the treated glass taught by Southern would thus allow more efficient assays.

Response to arguments

The response asserts at the top of page 18, that Southern does not cure the deficiencies of Huang and Voelker. Southern is solely being relied upon solely for its teaching of a glass support and thus was not needed to address any deficiencies of Huang and Voelker. Thus this rejection is maintained.

Summary

No claims are allowed over prior art cited.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, Art Unit 1634